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Editorial Comment

EDITORIAL COMMENT

Treatment of idiopathic membranous nephropathy in adults: KDIGO 2012, cyclophosphamide and cyclosporine A are out, rituximab is the new normal

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ABSTRACT

The 2012 Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guidelines for glomerulonephritis shed light on the complex world of glomerulonephritis therapy. However, they may no longer apply to idiopathic membranous nephropathy, as recently concluded by the KDIGO 2019 Working Group. This is due to the discovery of autoantibodies such as anti-phospholipase A2 receptor (anti-PLA2R) that allow disease monitoring as well as to results from recent clinical trials, comparative cohort studies and meta-analyses. Perhaps the most disruptive of them is the Membranous Nephropathy Trial of Rituximab (MENTOR) trial comparing rituximab with cyclosporine A, which supports the superiority of rituximab in efficacy and safety. Furthermore, rituximab results compared favourably with the short-term results of classical clinical trials that supported the KDIGO 2012 recommendation of immunosuppressive cyclophosphamide-based regimens as first choice for active treatment of idiopathic membranous nephropathy. Thus, the KDIGO recommendations for cyclophosphamide-based regimens or calcineurin inhibitors as the first line of active treatment regimens for idiopathic membranous nephropathy with nephrotic syndrome may no longer apply. By contrast, rituximab-based regimens or other B-cell-targeted therapies appear to represent the present and future of membranous nephropathy therapy.

Keywords: calcineurin inhibitors, cyclophosphamide, cyclosporine, membranous nephropathy, rituximab, treatment

INTRODUCTION

Idiopathic membranous nephropathy is the most common cause of nephrotic syndrome in white adults [1]. The autoantibody responsible for the characteristic immune deposits has been identified as anti-phospholipase A2 receptor (anti-PLA2R) in >70% of cases. Less frequently, the disease is caused by anti-thrombospondin type-1 domain-containing 7A (anti-THSD7A) (7%) or as yet unidentified antibodies [2]. Despite advances in understanding the pathogenesis, therapy remains controversial. As it is a rare disease, clinical trials are usually small and with a short follow-up. Additionally, the natural course is very variable, ranging from spontaneous remission to severe nephrotic syndrome progressing to end-stage kidney disease (ESKD). In July 2019, the results of the Membranous Nephropathy Trial of Rituximab (MENTOR) trial comparing rituximab versus cyclosporine A were published [3]. These results support the superiority of rituximab in efficacy for achieving remission of proteinuria and in safety. We believe this will bring a major paradigm shift in how the disease is treated, rendering the Kidney Disease: Improving Global Outcomes (KDIGO) 2012

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recommendations obsolete [4]. We now comment on the potential impact of MENTOR on routine clinical management of idiopathic membranous nephropathy and try to anticipate future changes in international guidelines.

WHAT DID KDIGO 2012 SAY ABOUT THERAPY OF IDIOPATHIC MEMBRANOUS NEPHROPATHY IN ADULTS?

The KDIGO 2012 recommended that initial therapy with immunosuppressants be started only in patients with nephrotic syndrome AND when at least one of the following conditions is met [4]:

(i) Urinary protein excretion persistently exceeds 4 g/day AND remains at >50% of the baseline value, AND does not show progressive decline during antihypertensive and antiproteinuric therapy during an observation period of at least 6 months.

OR

(ii) Presence of severe, disabling or life-threatening symptoms related to the nephrotic syndrome.

OR

(iii) Serum creatinine (sCr) has risen by ≥30% within 6–12 months from the time of diagnosis but the estimated glomerular filtration rate (eGFR) is not lower than 25–30 mL/min/1.73 m^2 AND this change is not explained by superimposed complications.

Thus, immunosuppressants may be initiated immediately if there is severely symptomatic nephrotic syndrome; otherwise, a waiting period of 6–12 months is suggested, and immunosuppressants are only initiated if there is persistently very high proteinuria despite antiproteinuric therapy for 6 months or sCr increases ≥30% (e.g. from 0.6 to 0.8 mg/dL or from 1.8 to 2.4 mg/dL, with 2.4 mg/dL being equivalent to 30 and 23 mL/min/1.73 m^2 in a 50-year-old male and female, respectively) spontaneously in these 6–12 months (Figure 1A). Antiproteinuric therapy implies renin–angiotensin system (RAS) blockade. However, KDIGO 2012 recommended that immunosuppressive therapy should not be used in patients with an sCr persistently >3.5 mg/dL (equivalent to eGFR 19 mL/min/1.73 m^2 or 14 mL/min/1.73 m^2 in a 50-year-old white male and female, respectively) or an eGFR <30 mL/min/1.73 m^2 AND reduced kidney size on ultrasound (e.g. <8 cm in length) OR those with concomitant severe or potentially life-threatening infections.

The initial recommended therapy was a 6-month course of alternating monthly cycles of oral and intravenous (i.v.) corticosteroids, and oral alkylating agents, and further suggested using cyclophosphamide rather than chlorambucil as initial alkylating agent. Then KDIGO 2012 recommended that patients be managed conservatively for at least 6 months following the completion of this regimen before being considered a treatment failure if there was no remission, unless kidney function was deteriorating or severe, disabling or potentially life-threatening symptoms related to the nephrotic syndrome were present. There was a suggestion to adjust the dose of cyclophosphamide or chlorambucil according to the patient's age and eGFR. It further suggested that continuous daily (non-cyclical) use of oral alkylating agents may also be effective but can be associated with greater risk of toxicity, particularly when administered for >6 months.

As alternative regimens for initial therapy, KDIGO recommended calcineurin inhibitors (CNIs) cyclosporine A or tacrolimus for at least 6 months in patients who choose not to receive the cyclical corticosteroid/alkylating agent regimen or who have contraindications to this regimen. It further suggested that CNIs be discontinued in patients who do not achieve complete or partial remission after 6 months of treatment. It further suggested that the dosage of CNI be reduced at intervals of 4–8 weeks to a level of ~50% of the starting dosage, provided that remission is maintained, and no treatment-limiting CNI-related nephrotoxicity occurs for at least 12 months.

For the treatment of idiopathic membranous nephropathy resistant to recommended initial therapy, KDIGO 2012 suggested using the alternative regimen. It further suggested that relapses of nephrotic syndrome be treated by reinstitution of the same therapy that resulted in initial remission. If a 6-month cyclical corticosteroid/alkylating agent regimen was used for initial therapy, the regimen was suggested to be repeated only once for treatment for a relapse.

Thus, KDIGO 2012 does not consider rituximab, despite successful experiences reported since 2002, as these were not part of formal clinical trials [5], but considers cyclophosphamide/corticosteroids or CNIs as potential first-line, alternative regimens.

WHAT WAS THE EVIDENCE TO RECOMMEND ALKYLATING AGENTS AND TO SUGGEST CYCLOPHOSPHAMIDE AS THE PREFERRED IMMUNE-SUPPRESSIVE AGENT?

The KDIGO 2012 provides a table summary of the evidence supporting the recommendation [4]. Since MENTOR conclusively demonstrated the superiority of rituximab over cyclosporine A, let us review the evidence supporting the recommendation of cyclophosphamide/corticosteroids. A meta-analysis mixing different alkylating regimens, randomized controlled trials (RCTs) testing chlorambucil and one RCT using cyclophosphamide are cited as evidence for recommending alkylating agents and for suggesting the use of cyclophosphamide. From our point of view, different drugs with different dosing regimens, different safety profile and very different follow-up periods should not be mixed in a meta-analysis, even if both are alkylating agents. This was useful in the face of scarce evidence available consisting of small trials with short follow-up, but is no longer admissible when other drugs have provided solid evidence of efficacy in well-run RCTs with an active comparator. Thus, we focus on the individual evidence supporting the use of cyclophosphamide/corticosteroids.

The open-label randomized study cited by KDIGO 2012 to support cyclophosphamide use compared the experimental regimen (methylprednisolone i.v. 1 g/day for three consecutive days followed by oral prednisolone 0.5 mg/kg/day for 27 days in the first, third and fifth months and oral cyclophosphamide at 2 mg/kg/day in the second, fourth and sixth months, with an approximate total dose of 13.5 g) versus supportive therapy (dietary sodium restriction, diuretics and antihypertensive agents excluding RAS blockade) in adults with nephrotic syndrome (proteinuria >3.5 g/day) caused by biopsy-proven idiopathic membranous nephropathy of ≥6-month duration, and patients were followed for at least 10 years [6] (Table 1). The article states that 'study endpoints were doubling of sCr, development of ESRD, or mortality', but it does not indicate which were primary and which were secondary endpoints. The Results section

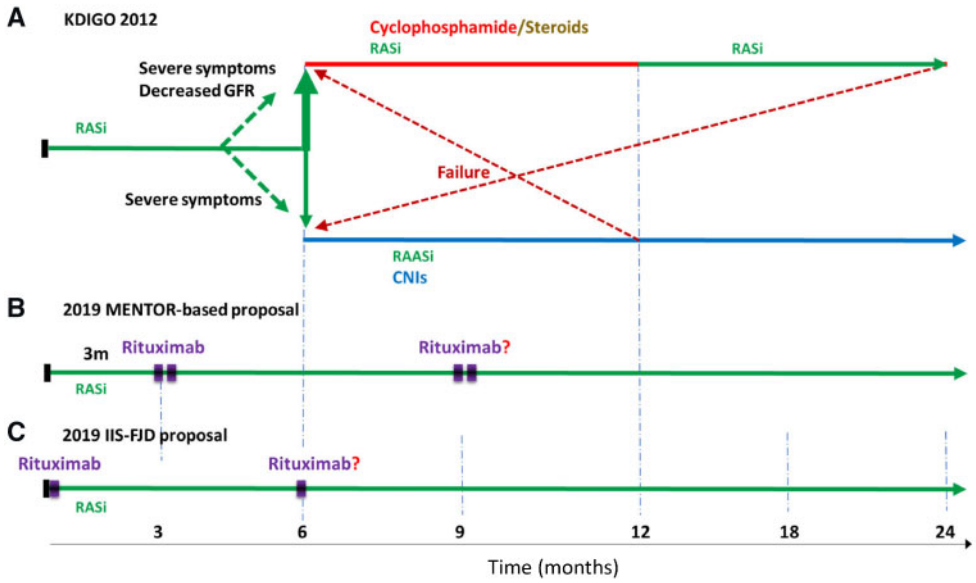

FIGURE 1: The KDIGO 2012 recommendations for treatment of idiopathic membranous nephropathy in adults and the 2019 MENTOR-based shift of paradigm. **(A)** The KDIGO 2012 recommendations for treatment of idiopathic membranous nephropathy [4]. Two alternative immunosuppressive regimens are proposed if there is no initial response to antiproteinuric therapy for 6 months. Immunosuppression may be started earlier if nephrotic syndrome is very symptomatic or eGFR decreases. Cyclophosphamide/steroids are preferable as the first choice over CNIs. Cyclophosphamide/steroids are maintained for 6 months but are not considered to have failed until Month 12. If at this point in time there is failure, CNIs are the alternative. CNI therapy is considered a failure if no remission is achieved within 6 months, at which point, cyclophosphamide/steroids are proposed as an alternative. If remission is achieved, CNI should be maintained for at least 12 months. Given the high recurrence rate upon withdrawal, CNI dose is decreased over time. **(B)** The 2019 MENTOR-based change of paradigm for treatment of idiopathic membranous nephropathy [3]. Rituximab is administered as two consecutive 1 g doses separated by 2 weeks that may be repeated at 6 months when there has been no response to antiproteinuric therapy for 3 months. This regimen was shown to be superior in efficacy achieving remission and safety, maintaining better renal function than cyclosporine A, a CNI. **(C)** Alternative proposal for rituximab-based idiopathic membranous nephropathy therapy. Based on the lag-time to complete remission since initial rituximab dosing and the safety profile of rituximab, this proposal is aimed at minimizing complications from nephrotic syndrome. The use of a single dose of rituximab may limit the economic impact of rituximab, and the earlier start of rituximab may result in a shorter nephrotic syndrome exposure. RASi, renin–angiotensin system inhibitors; IIS-FJD, Instituto Investigación Sanitaria Fundación Jiménez Díaz.

suggests that this may be a combined endpoint. Although it is stated that the analysis was performed with an intention-to-treat (ITT) basis, patients who were lost in follow-up from 18 to 48 months were excluded from analysis and no baseline or even short-term remission results were reported. One hundred and four patients were recruited from 1993 to 1995: 53 control and 51 active therapy, but 11 were lost in follow-up and were not analysed (11% of the initial sample). Thus, the analysis cannot be considered either ITT or modified ITT. The power of the study and sample size calculations were not specified. Whether there was a pre-specified follow-up is also unclear from the report. The cohort was younger (mean age 37–38 years) than European or American cohorts. There was no apparent exclusion criterion based on eGFR. Initial remission (<2 g/day or <50% of baseline, along with normal sCr) was achieved within 1 year of randomization in 5/53 (9%) and 15/51 (29%) of ITT patients in control and experimental groups, respectively, and ever remission in 16/53 (30%) and 34/51 (67%), respectively. Of these, 5/53 (9%) and 15/51 (29%) were complete remissions at 10 years. Thus, overall, cyclophosphamide/steroids achieved a complete remission in an additional 20% of patients, on top of spontaneous complete remissions observed with supportive therapy that initially excluded RAS blockade (Figure 2A and B; Supplementary data, Figure S1). Complete remissions on active therapy were observed in <10% of patients at 12 months. The proportion of patients on complete remission continued to increase up to ~40 months and then stabilized (Figure 2C and D). Relapses occurred in 4/16 (25%) and 8/34 (24%) for control and cyclophosphamide/steroids patients, respectively, 5.4 ± 6.2 months after the first remission in those on cyclophosphamide/steroids (Figure 2E). These patients were treated with addition of RAS blockade. A total of 13/53 (25%) supportive therapy patients and 30/51 (59%) cyclophosphamide/steroids patients were in remission until the time of final follow-up. However, these and safety data were confounded by prescription of immunosuppressive regimen 24 months after randomization in 15/53 (28%) supportive therapy patients. Treatment of the control cohort would not have been considered standard today since RAS blockade was prohibited initially and only prescribed to 17/53 (32%) at 2 years and this increased to 32/53 (60%) at 10 years.

The trial also reported long-term outcomes. For the first 7 years, the incidence of renal replacement therapy was low and there were no differences between the groups (<5% in both groups). However, the 10-year dialysis-free survival was 65% and 89% of the analysed patients in the control and treatment groups, respectively ($P = 0.016$). The combined endpoint was significantly more frequent in the control analysed patients and started to diverge at ~6 years. At 20 months of follow-up, eGFR was similar in both groups but then diverged. At 1 year, proteinuria in the analysed patients of the intervention group was >3 g/day. Timing considerations are important when interpreting results from other therapeutic regimens that lack the long-term follow-up.

It is also worth mentioning a prior Ponticelli *et al.* study [7] of cyclophosphamide/steroids with primary endpoint not specified and a shorter follow-up, without clarification of whether there was a pre-specified follow-up, in which the comparator was chlorambucil/steroids and no ITT data were presented. Excellent overall remission results were observed at 1 year and they continued to improve up to 5 years, but these results were at odds with other cyclophosphamide/steroids studies and the difference may likely be traced back to the inclusion of patients

Table 1. Patient characteristics and results of three major randomized clinical trials in primary membranous nephropathy

	Ponticelli *et al.* [7]	Jha *et al.* [6]	MENTOR, Fervenza *et al.* [3]
Requirement for pre-RCT follow-up	None	6 months	3 months of RAS blockade
Test drug	Methylprednisolone, prednisolone and cyclophosphamide	Methylprednisolone, prednisolone and cyclophosphamide	Rituximab
Comparator	Methylprednisolone, prednisolone and chlorambucil	Dietary sodium restriction, diuretics and antihypertensive agents. RAS blockade excluded	Cyclosporine A
RAS blockade	Discouraged	Prohibited	Required
Primary endpoint	Unclear	Unclear. Endpoints included doubling of sCr, development of ESRD or patient death	Composite of complete or partial remission at 24 months
Pre-specified follow-up	Not reported	Unclear. Patients were followed for ≥10 years, but unclear whether this was pre-specified. Totally, 28% of control patients eventually received the test drug	24 months
Duration of test drug therapy	6 months	6 months	2 weeks, could be repeated at 6 months
Follow-up (years)	≥1	≥10	2
N on experimental regimen	45	51[a]	65
Age (years)	48	37±12	52±13
Upper age limit (years)	65	None	80
Baseline eGFR (mL/min/1.73 m^2)	76[b]	84±22	85±30 (Ccr)
eGFR inclusion criterion (mL/min/1.73 m^2)	≥42[c]	No data	≥40
Baseline proteinuria (g/24 h)	6.8 ± 3.5	5.9±2.2	8.9 (6.7–12.9)
Proteinuria inclusion criterion (g/24 h)	>3.5	>3.5 without RAS blockade	>5.0 on RAS blockade
Remission at 1 year, *n*/*N* (%)	40/45 (89)	15/51 (29)	39/65 (60)[d]
Complete remission, *n*/*N* (%)	16/45 (35.5), peak at 60 months	15/51 (29) peak at 40–45 months	23/65 (35). End of follow-up at 24 months
Complete remission at 24 months, *n*/*N* (%)	∼20%[e]	∼25%[e]	23/65 (35%)
Relapses, *n*/*N* (%)	10/40 (25)	8/34 (24) within 5±6 months of first remission	2/39 (5) at 24 months
Definitions			
Partial remission	0.2–2 g/day	0.2–2 g/day or <50% of baseline	Decrease 50% from baseline plus final proteinuria 0.3–3.5 g/day
Complete remission, definition	<0.2 g/day	<0.2 g/day	<0.3 g/day

Key RCTs defining how membranous nephropathy is treated have been published in the past 20 years, with approximately one-decade separation between them. Baseline data and outcome data are shown for the intervention group. Baseline proteinuria presented as mean ± SD or median (interquartile range).
[a]Fifty-one randomized to test therapy, but four lost to follow-up and no baseline data provided for these four patients.
[b]Estimated by applying the CKD-EPI equation to mean sCr adjusted by age and sex distribution of participants.
[c]Estimated by applying the CKD-EPI equation to the cut-off sCr of 1.7 mg/dL adjusted by age and sex distribution of participants.
[d]Values at 24 months (primary endpoint) were the same.
[e]Estimated from figures in the article.
Ccr, creatinine clearance; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; ESRD, end-stage renal disease.

just after diagnosis in Ponticelli *et al.* study [7] without a prior expectant attitude towards spontaneous remission (Table 1). Indeed, the rate of complete remission was lower and in line with Jha *et al.* [6] (Figure 2C and D). The use of RAS blockade was discouraged and the relapse rate of 25% for cyclophosphamide/steroids was in line with the study by Jha *et al.* [6, 7] (Figure 2E).

As a summary of the evidence supporting the prescription of cyclophosphamide/steroids, these RCTs would be hardly admissible as evidence under current standards, given the outdated methodology used, without clarification of pre-specified endpoints or follow-up time; the suboptimal symptomatic therapy, which discouraged or prohibited RAS blockade; and other peculiarities of the studies, such as the younger than usual population or the lack of an expectant, symptomatic therapy period before initiation of immunosuppression. In any case, the short-term information gathered from these cyclophosphamide/steroids studies can be summarized as follows: induction of complete remission in ∼20–25% of patients at 24 months, a peak complete remission of ∼30–35% in months 40–60 of follow-up (for the study that had a control comparator, this represents 20% above the control group) and a relapse rate of 25% (Table 1; Figure 2A–E).

WHAT DO RECENT META-ANALYSES SHOW?

In a 2017 network meta-analysis of RCTs (thus excluding rituximab), cyclophosphamide, cyclosporine A or tacrolimus

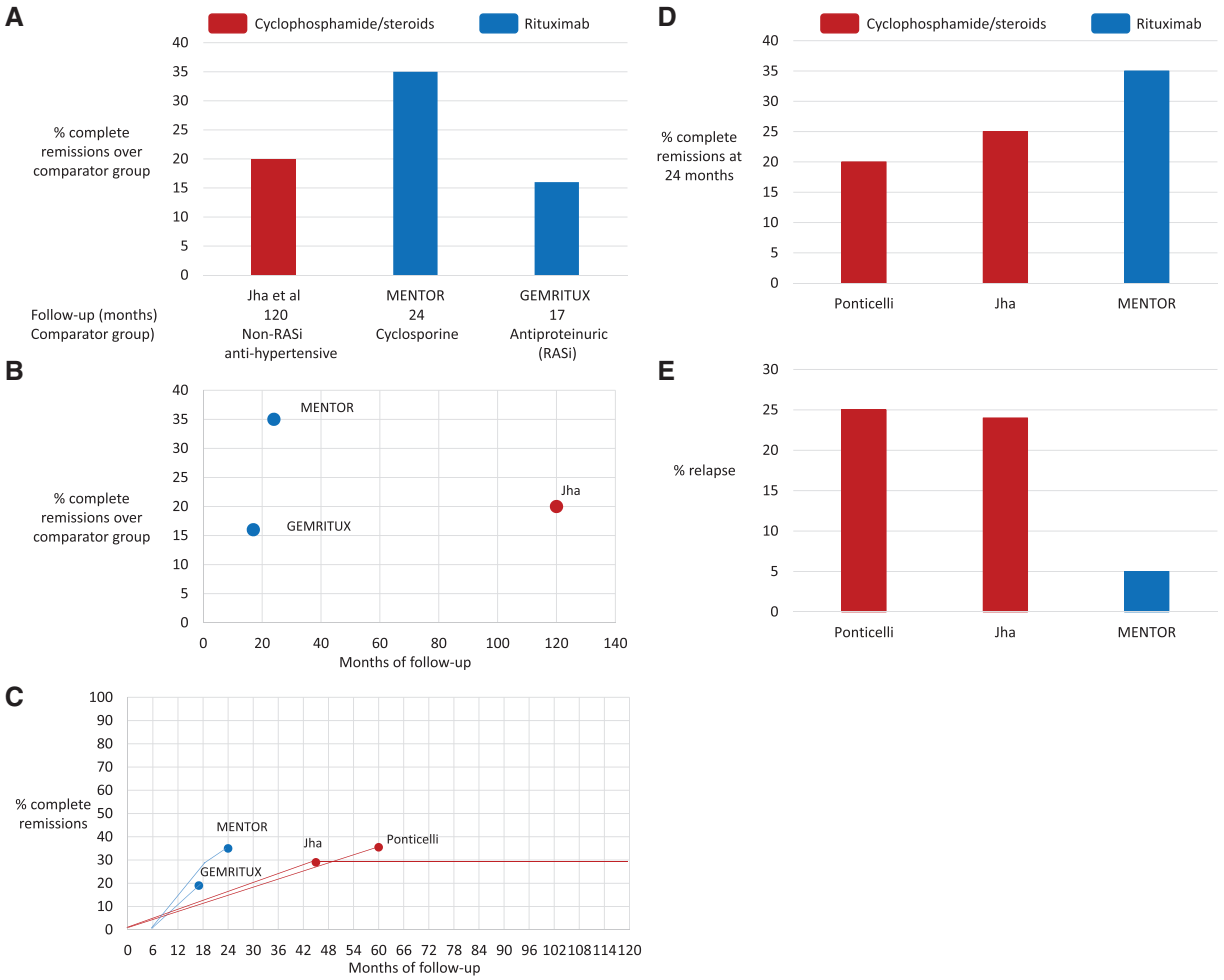

FIGURE 2: Complete remissions in key randomized clinical trials of immunosuppressive therapy in idiopathic membranous nephropathy. (**A**) The percentage of complete emissions is shown and the time point at which these were assessed is indicated. The percentage of remissions observed in the comparator group has been subtracted from the percentage in the intervention group. In Jha *et al.* [6], RASi were allowed only after 12 months but were only prescribed in up to 60% of patients. (**B**) Percentage of complete remissions over comparator group versus time of follow-up at which they were assessed. In the Jha *et al.* study [6], complete remission continued to occur in the intervention group up to Month 45 and in the control group up to Month 60. Thus, the same graph as in (B) but assigning a 60-month follow-up to this study is shown in Supplementary data, Figure S1. (**C**) Time course of complete remissions. Percentage of complete remissions in the intervention group without subtracting control group complete remissions. ITT analysis. No remissions were noted in MENTOR at 6 months or in GEMRITUX. Please note that maximum follow-up was 24 months in MENTOR and upper quartile follow-up was 23 months in GEMRITUX, so data are incomplete regarding later time points. Time-course graphs for Ponticelli *et al.* [7] and Jha *et al.* [6] were presented in their manuscripts and indicated that some complete remissions had occurred by 6 months. Complete remissions appear to have a lag period of ~6 months for rituximab, but then they increase faster than for cyclophosphamide/steroids. The timing of complete remission plateau under rituximab is unclear from these data. (**D**) Complete remissions at 24 months, without subtracting control group complete remissions. GEMRITUX data are not presented, since the upper quartile follow-up was 23 months. (**E**) Relapse rate. GEMRITUX data are not presented, since the upper quartile follow-up was 23 months. Rituximab is shown in blue and cyclophosphamide/steroids in red. Jha *et al.* [6] data were presented on an ITT basis, except for (D), in which they were estimated from a graph, and thus represent patients with available data. The definition of complete remission and percentage of complete remissions in the comparator group were as follows: Ponticelli *et al.* and Jha *et al.*: proteinuria <0.2 g/day, complete remissions in comparator group in Jha *et al.* 5/53 (9%), in Ponticelli *et al.* comparator was chlorambucil/steroids, and thus the Ponticelli *et al.* data are not used when assessing complete remission minus control complete remissions; MENTOR: proteinuria <0.3 g/day, complete remissions in comparator group none; GEMRITUX: proteinuria <0.5 g/day, complete remissions in comparator group 1/38 (3%) [3, 6–8]. RASis, renin–angiotensin system inhibitors.

significantly increased the rate of complete or partial remissions as compared with non-immunosuppressive treatment, but there were no significant differences in the probability of remission between cyclosporine A and cyclophosphamide, while drug withdrawal was more likely with cyclophosphamide than with cyclosporine A or tacrolimus [9]. Compared with non-immunosuppressive treatment, of these drugs only cyclophosphamide significantly reduced the risk of a composite outcome of mortality or ESKD [odds ratio = 0.31, 95% confidence interval 0.12–0.81], but there were no significant differences between cyclophosphamide and CNIs. This result may have been biased by the lack of long-term studies with CNIs that had a follow-up of 12–18 months, which limits the ability to test impact on these long-term outcomes (differences in mortality or ESKD versus antihypertensive therapy were not observed for cyclophosphamide-based regimens in the first 6–7 years of follow-up) [6].

WHAT DID KDIGO 2019 SAY?

The recent report of the KDIGO controversies conference on management and treatment of glomerular diseases concluded

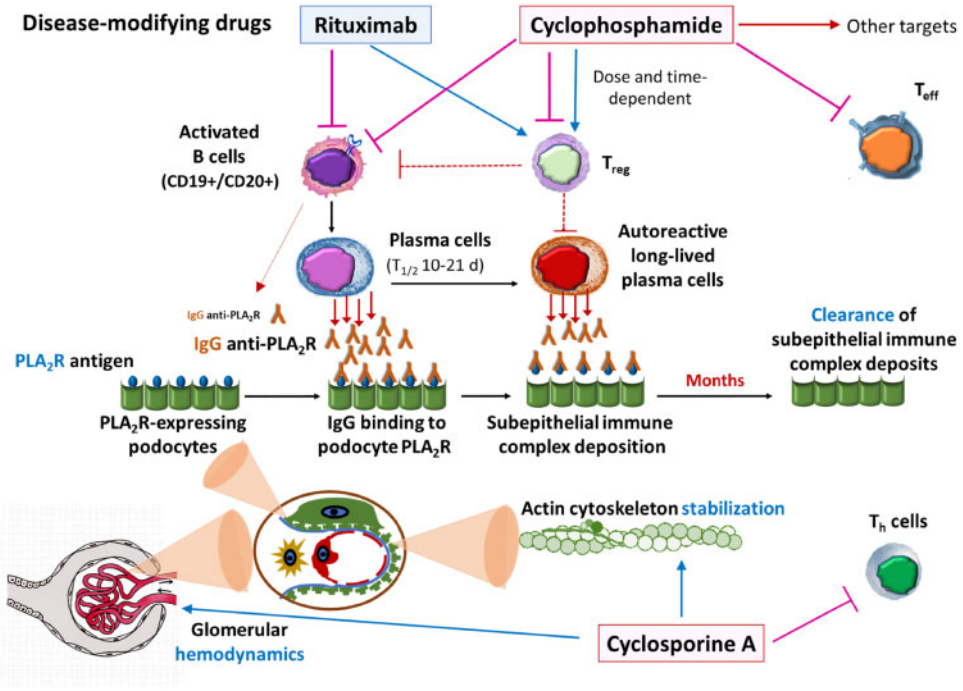

FIGURE 3: Pathogenesis of membranous nephropathy and mechanism of action of rituximab, CNIs and cyclophosphamide: working hypothesis to explain the timing of response and different clinical impact. Idiopathic membranous nephropathy is an autoimmune disease caused by autoantibodies that bind to the podocyte cell surface antigen PLA2R, leading to podocyte injury and sub-epithelial immune complex deposits that may take months to clear after total cessation of antibody production. B cells may already produce immunoglobulin G (IgG), but the bulk of it is produced by more mature plasma cells, which usually have a half-life of a few weeks to months. However, a few plasma cells are long-lived and continue to produce antigen-specific IgG. Regulatory T cells (T_{regs}) prevent the emergence of these long-lived plasma cells and suppress activated B cells [11]. Plasma cells are not rituximab targets. Rituximab binds to and kills CD20-expressing B cells. B-cell death may involve different molecular mechanisms but complement-mediated cell death appears to be important since cell culture studies have identified specific complement regulatory protein that confers resistance to rituximab-induced B-cell death [12]. Additionally, membranous nephropathy patients responding to rituximab display an upregulation of T_{regs}, which is not present in patients not responding or in controls [13]. Cyclophosphamide selectively targets T, B and other lymphocytes over other cell types, as they have the molecular machinery to activate cyclophosphamide through a β-elimination reaction [14]. However, it has off-target effects in multiple other cell types, and the impact of cyclophosphamide on T_{regs} is dose and time sensitive [15]. This variable impact of cyclophosphamide on T_{regs}, in which lower doses may actually inhibit T_{regs} [16], may underlie the relatively high relapse rate as opposed to rituximab. Finally, cyclosporine A is a T cell immunosuppressive drug that additionally has glomerular haemodynamic effects, decreasing GFR and proteinuria, as well as an actin cytoskeleton-stabilizing effect on podocytes that may also contribute to decrease proteinuria [17]. Frequent need for continuous administration of the drug to maintain remission points is an important contribution of direct impact on glomerular haemodynamics and podocytes, which require continuous presence of the drug. From this point of view, rituximab and cyclophosphamide may be considered disease-modifying drugs, but the use of this term for cyclosporine A may be disputed.

that nearly all of the KDIGO 2012 membranous nephropathy recommendations should be revisited based on the discovery of podocyte antigen targets of circulating antibodies and on recent clinical studies and trials [4, 10]. We agree with this assessment.

WHAT DID THE MENTOR TRIAL OF RITUXIMAB VERSUS CYCLOSPORINE A SHOW?

In July 2019, the MENTOR trial of rituximab versus cyclosporine A for idiopathic membranous nephropathy in adults was published [3]. MENTOR randomized 130 membranous nephropathy patients with proteinuria ≥5 g/day despite at least 3 months of RAS blockade, and an eGFR ≥40 mL/min/1.73 m^2 to receive oral cyclosporine A for 12 months or two rituximab infusions, 1000 mg each, administered 14 days apart and repeated at 6 months in case of partial response. The primary outcome was a composite of complete or partial remission of proteinuria at 24 months (Table 1). At 24 months, 39/65 patients (60%) in the rituximab group and 13/65 (20%) in the cyclosporine A group had a complete or partial remission ($P < 0.001$). Additionally, at 24 months, 23 rituximab patients (35%) and no cyclosporine A patient had a complete remission (Figure 2A–D). Among patients who achieved remission, the decline in anti-PLA2R antibodies was faster and larger in the rituximab group, suggesting that rituximab-induced immunological remission precedes kidney remission. Serious adverse events tended to be less common with rituximab [11/65 (17%) versus 20/65 (31%); $P = 0.06$], which better preserved kidney function.

While MENTOR did not directly compare rituximab with cyclophosphamide, the results were similar to or better than historical RCTs that formed the basis of the KDIGO 2012 recommendation of alkylating agents and preferably cyclophosphamide in association with steroids as the first line of therapy for idiopathic membranous nephropathy (Figure 2A–E) [6, 7]. Thus, although the onset of complete remissions induced by rituximab may have a lag time of at least 6 months from the start of therapy (Figure 2C), both the overall rate of complete remissions at 24 months and the excess rate of complete remissions over controls were higher for rituximab than for key prior cyclophosphamide/steroids trials and the relapse rate on rituximab at 5% was well below that reported previously for cyclophosphamide/steroid studies (Table 1; Figure 2A–E). However, the different definitions of remission used complicate the interpretation of these data. Although we lack long-term follow-up data

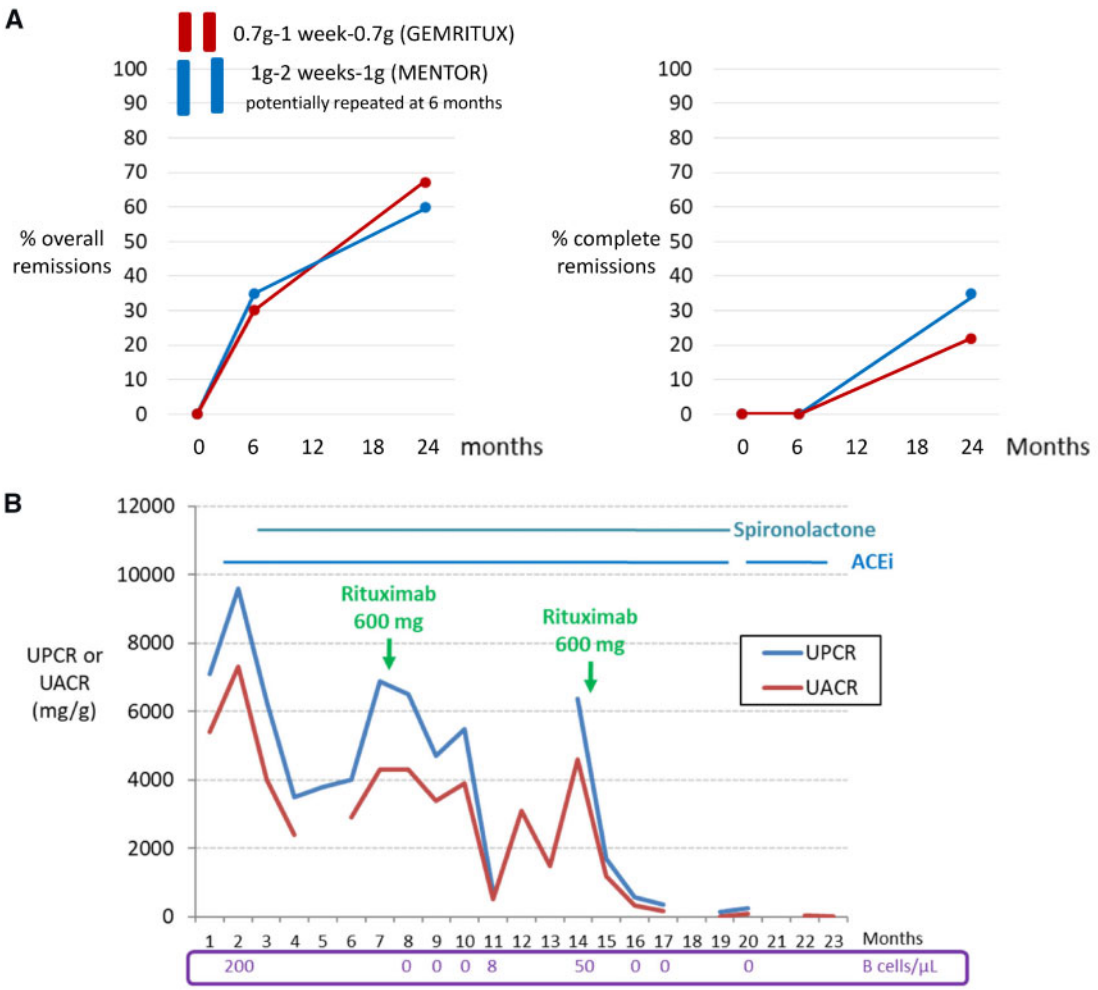

FIGURE 4: Rituximab dosing and remissions. (**A**) Different initial dosing regimens used by GEMRITUX (two 375-mg/m^2 infusions separated by 1 week, total dose 1.45 g) and MENTOR (two 1-g infusions separated by 2 weeks, total dose 2 g) resulted in similar complete remissions and overall remissions from 6 to ~24 months of follow-up. In MENTOR, dosing could be repeated after 6 months. There were no statistically significant differences. Both populations had similar age and GFR, but proteinuria was numerically higher in GEMRITUX [3, 20]. Graphs were constructed using only 6- and 24-month time points. For GEMRITUX, data used were from anti-PLA2R-positive patients from Seitz-Polski *et al.* [20], since they provide complete remission data at 6 months. (**B**) Impact of single-dose rituximab: clinical course. A 56-year-old normotensive woman was diagnosed with nephrotic syndrome with preserved eGFR (103 mL/min/1.73 m^2) because of primary membranous nephropathy. RAS blockade [angiotensin-converting enzyme inhibitor (ACEi) plus spironolactone] was instituted. Initially, proteinuria decreased >50% but remained at 3500 mg/g with persisted nephrotic syndrome. Then proteinuria again increased progressively and a single dose of rituximab 375 mg/m^2 was administered. This achieved peripheral blood B-cell depletion for >3 months and partial remission of proteinuria (nadir 525 mg/g). A second rituximab dose was administered 7 months after the first dose because of recurrent nephrotic syndrome and resulted in peripheral blood B-cell depletion for >5 months and complete remission. In the latest follow-up, albuminuria is undetectable. Overall, the patient received 1.2 g of rituximab. No adverse effects were noted. UPCR, urinary protein–creatinine ratio; UACR, urinary albumin–creatinine ratio.

for rituximab, both the higher percentage of complete remissions and the lower relapse rate bode well for long-term outcomes.

WHAT WERE THE SHORTCOMINGS OF THE GEMRITUX TRIAL OF RITUXIMAB VERSUS CONVENTIONAL ANTIPROTEINURIC TREATMENT ALONE?

GEMRITUX was a prior, recent and smaller ($n = 75$) trial with shorter follow-up (6 months for the primary endpoint) of rituximab versus conventional antiproteinuric treatment [8]. All patients received conventional antiproteinuric treatment and rituximab was administered in two 375-mg/m^2 i.v. infusions 7 days apart to 37 patients. From an evidence-based medicine point of view, GEMRITUX was disappointing since it missed the primary endpoint: at Month 6, 13 (35%) patients on rituximab and 8 (21%) patients on conventional antiproteinuric treatment achieved a complete or partial remission ($P = 0.21$). Thus, rituximab appeared no different than antiproteinuric therapy alone. However, the design of this study was severely flawed and not adjusted to the current understanding of the pathogenesis of membranous nephropathy and the mechanism of action of rituximab (Figure 3) [18]. Thus, rituximab reduces the number of B cells and this results in a progressive decrease in circulating antibody titers, the same antibodies that are deposited in the subepithelial space. However, even if antibody deposition ceases suddenly, sub-epithelial deposits are long-lived, so a slow and progressive decrease in deposits and proteinuria is expected [19]. Thus, the 6-month time point was unrealistic for therapeutic success as further supported by zero complete remissions observed in MENTOR at this time point (Figure 4A). Fortunately,

Table 2. Dose and administration regimens of rituximab for idiopathic membranous nephropathy

	NICE [20]	MENTOR [3]	GEMRITUX [20]	GEMRITUX [8]
Design	Retrospective cohort (observational)	RCT	RCT	RCT
N for rituximab group	28	65	27[a]	37
Initial rituximab dose	2 × 1 g, 2-week interval	2 × 1 g, 2-week interval	2 × 375 mg/m^2, 1-week interval (total dose 1.45 g)	2 × 375 mg/m^2, 1-week interval
Mean age (years)	63	52	51	53
Baseline proteinuria (g/g)[b]	5.9	6.2	8.4	7.7
Overall remissions 6 months, *n*/N (%)	18/28 (64)	23/65 (35)	8/27 (30)	13/37 (35)
Complete remission 6 months, *n*/N (%)	5/28 (18)	0/65 (0)	0/27 (0)	No data
Overall remissions end of follow-up, *n*/N (%)	24/28 (86) at median 15 months	39/65 (60) at 24 months	18/27 (67) at median 24 months	24/37 (65) at median 17 months
Complete remissions end of follow-up, *n*/N (%)	9/28 (32) at median 15 months	23/65 (35) at 24 months	6/27 (22) at median 24 months No statistically significant difference versus NICE or MENTOR	7/37 (19) No statistically significant difference versus NICE or MENTOR

Data from clinical trials and an observational cohort. Note that age was similar for MENTOR and GEMRITUX, GFR was similar for all groups (not shown). NICE, National Institute for Health and Care Excellence.

[a]Only anti-PLA2R-positive patients in this analysis.

[b]For MENTOR, please note that in Table 2, proteinuria is expressed in g/g urinary creatinine but in Table 1 it is expressed in g/day.

Table 3. Unmet clinical needs and unanswered questions in the treatment of primary membranous nephropathy

- Relative position of rituximab versus cyclophosphamide/steroids as the first-line therapy
- Long-term rituximab outcomes: preservation of renal function and progression to ESKD
- Timing of initial rituximab indication
- Optimal dosing of rituximab
- Adjuvant therapy to accelerate remission while the disease-modifying effect of rituximab sets in
- Alternative regimens for rituximab treatment failures or improve rituximab efficacy record without compromising safety
- Role of serum anti-PLA2R antibodies specificity or titer in the individualization of immunosuppressive therapy

the study provided a *post hoc* observational follow-up of a median of 17 months from inclusion. At the end of this period, 24 of 37 (65%) rituximab and 13 of 38 (34%) conventionally treated patients were on remission ($P < 0.01$). Complete remissions were observed in 7/37 (19%) and 1/38 (3%) rituximab and antiproteinuric patients, respectively ($P = 0.03$). These numbers are in line with the MENTOR data (Figures 2B and C, and 4A; Supplementary data, Figure S1). Median times to remission were 7.0 (interquartile range 5.5–10.5) months ($n = 24$) and 7.0 (4.0–13.0) months ($n = 13$) in the rituximab and the antiproteinuric treatment groups, respectively. There were no safety differences between the two regimens, further supporting, together with MENTOR, the safety of rituximab.

RITUXIMAB DOSE OPTIMIZATION

Both MENTOR and GEMRITUX tested a multiple dose rituximab regimen: two consecutive 1-g doses separated by 2 weeks and two consecutive 375-mg/m^2 doses separated by 1 week, respectively [3, 8] (Figure 4A). Rituximab was originally authorized to treat lymphoma and later rheumatoid arthritis at doses of 375 mg/m^2 weekly for 4 weeks (total dose of 1.73 m^2 individual: 2.6 g = 4 × 0.65 g) for lymphoma and 1 g repeated 2 weeks later (total dose 2 g) for rheumatoid arthritis. Idiopathic membranous nephropathy regimens and RCTs just copied and adapted these authorized and tested regimens. However, the key question is whether the repeated initial dosing is necessary for membranous nephropathy. This is a question worth asking since one of the limitations to a more widespread use of rituximab is cost, even though cost analysis has concluded that rituximab may be cost-effective in the short and medium terms compared with cyclophosphamide/steroids [21]. However, health and hospital authorities quite often focus on the short-term and local hospital drug costs, and would put up barriers to prescribing rituximab when cyclophosphamide is cheaper. Additionally, a lower rituximab dose may be safer, although both MENTOR and GEMRITUX evidenced an excellent safety profile, similar to conventional antiproteinuric therapy and better than cyclosporine A. The Italian pioneers of rituximab for membranous nephropathy, Ruggenenti *et al.* [22], have long advocated a single-dose regimen termed as B-cell-driven rituximab treatment, in which a second single dose is prescribed based on B-cell depletion and proteinuria response [22]. In this regard, most membranous nephropathy patients will clear circulating B cells within 24 h of a single 375-mg/m^2 rituximab dose, questioning the need for initial repetitive dosing [23, 24]. Thus, the single-dose regimen may achieve long-term complete remission, or may be followed by a second single dose if B cells are not depleted or following recurrence or partial remission (Figure 4B).

Although a rituximab dose–response effect on the timing and frequency of remission was recently suggested based on comparison of independent studies (an observational study and

the anti-PLA2R positive patients in GEMRITUX) using different individual doses and timings between doses [20], inclusion of the MENTOR data in the comparison argues against such a dose–response relationship (Table 2; Figure 4A). Earlier, a higher rate of complete and/or overall remission was reported in the observational study using a total dose of 2 g with a 2-week interval between two 1-g doses than with a total dose of 1.45 g (375 mg/m^2 × 2) with a 1-week interval between doses in GEMRITUX (Table 2) [20]. The combination of higher dose and lower epitope spreading (a measure of how many epitopes in the PLA2R are recognized by anti-PLA2R antibodies in individual patients) was associated with remission [20]. However, when comparing GEMRITUX with MENTOR, which used the (higher dose) 1 × 2-g protocol, these putative differences in remission rates or timings were not apparent (Figure 4A).

ANY MORE NEWS ON THE HORIZON?

The RI-CYCLO trial, estimated to be completed by December 2019, is assessing the efficacy (primary endpoint complete remission at 1 year) and safety of rituximab versus cyclophosphamide/steroids in 76 patients with membranous nephropathy [25]. Another major trial, Sequential therapy with TAcrolimus and Rituximab in primary MEmbranous Nephropathy (STARMEN), was completed on 30 June 2019 [26]. STARMEN randomized 86 patients to sequential therapy with tacrolimus for 6–9 months plus single dose of rituximab (1000 mg i.v.) or cyclophosphamide/steroids. The primary endpoint was the proportion of patients reaching either complete or partial remission at 24 months. Other relevant endpoints were the time to achieve remission, number of relapses, doubling of sCr and the prognostic value of anti-PLA2R antibodies. The results of this trial are to be made public in late 2019 or 2020.

CONCLUSION

In conclusion, the MENTOR trial provided conclusive evidence of the higher efficacy of rituximab in inducing remission and its better safety than cyclosporine A, one of the regimens recommended by KDIGO 2012. These results should be a game changer and the future guidelines may likely recommend rituximab over CNIs.

However, unsolved issues remain (Table 3). One is the relative position of rituximab versus cyclophosphamide/steroids. Based on the published trials with cyclophosphamide/steroids, we believe that rituximab efficacy and safety compare favourably with these regimens. Although long-term trials are missing for rituximab, but available for cyclophosphamide/steroids, the success in inducing complete remission with rituximab is likely to result in improved long-term outcomes, although this remains to be demonstrated conclusively. In this regard, the long-term clinical trial of cyclophosphamide/steroids, on which the KDIGO 2012 recommendations are based, would probably not meet current management standards for proteinuric kidney disease in the placebo arm and the current RCT design and reporting standards [6]. Thus, this trial should be considered outdated. The results of ongoing or recently completed trials, RI-CYCLO and STARMEN, comparing cyclophosphamide/steroids with rituximab or rituximab/tacrolimus are awaited. For STARMEN, the complexity of the rituximab arm, which additionally includes tacrolimus, may impair its ability to represent the impact of rituximab alone.

Another unsolved issue is the optimal dosing of rituximab. The MENTOR regimen will likely become the standard approach to membranous nephropathy, given that it is supported by a clinical trial. However, regimens currently in use in membranous nephropathy are derived from those used in malignancy, and dosing could be further optimized. A lower optimized dose would entail significant cost savings and help to extend use of rituximab to more economically deprived healthcare systems.

Finally, treatment failure was observed in MENTOR in 26 (40%) rituximab patients and 52 (80%) cyclosporine A patients by 24 months. Thus, the current first-line therapeutic approaches fail to help a large number of patients. New B-cell–targeting therapies and other promising therapeutic approaches have been reviewed recently [18]. Additionally, an unmet clinical need is co-adjuvant therapy that may accelerate complete remission to a >3-month window, to be used in the time window that it takes for rituximab or other disease-modifying regimens to induce immunological remission and for this immunological remission to translate to clinical remission. In this regard, given the lag time from initiation of therapy to a response, the potential adverse consequences of persistent nephrotic syndrome and the safety profile of rituximab, an argument could be made to initiate therapy as soon as idiopathic membranous nephropathy is diagnosed (Figure 1C). A similar argument was made to justify immediate initiation of cyclophosphamide/steroids or chlorambucil/steroids, which represent a less safe alternative, >20 years ago [7].

SUPPLEMENTARY DATA

Supplementary data are available at ckj online.

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CONFLICT OF INTEREST STATEMENT

None declared.

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